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MafB is important for pancreatic β-cell maintenance under a MafA deficient condition

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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, XIAFUKAITI GULIBAIKELAMU describes the phenotypes of pancreatic beta cell-specific MAFA and MAFB double KO. The content is summarized as follows:

（目的　**Purpose**）

The author's laboratory has been investigating MAF family. Her project focused on the role of MAFB in relation to MAFA. Lifelong expression of MAFB in human pancreatic β-cells implies its involvement in maintaining mature β-cell function. Despite being a preferred mammalian model for biomedical research, mice do not express MafB in adult pancreatic β-cells. Interestingly, re-expression of MafB in the β-cells of adult MafA deficient mice was detected in the previous study, which implies potential role of MafB in mature β-cells under certain pathological condition in mice. Therefore, the purpose of this study was to investigate whether MafB can take part in adult mouse β-cell activity under MafA-deficient condition by generating MafA and MafB double knockout (A0B0) mice.

（対象と方法　Materials and Methods）

Using C57BL/6J mice strain, the author generated MafA and MafB double knockout (A0B0) mice in which MafB was specifically deleted from the pancreatic β-cells, and compared their phenotype with those of MafA single knockout (A0B2) and WT mice under normal diet and high fat diet (HFD) conditions. To compare the glucose metabolism of each mice group, fasting blood glucose level measurement, i.p. glucose tolerance test and glucose stimulated insulin secretion experiments were conducted at certain time points. To compare the islet morphology of the mice from different genotypes, immunohistochemistry and hematoxylin and eosin staining were performed together with the cell counting. Quantitative real-time PCR experiment was also done using islet derived cDNA to check gene expression.

（結果　**Results**）

The author observed that additional deletion of MafB aggravated the metabolic phenotype resulting from MafA single knockout mice. Under a normal diet condition, relatively more impaired glucose intolerance in A0B0 mice than A0B2 mice was observed. Sheconsidered that impaired glucose tolerance could be due to either the impaired insulin production and thus impaired insulin content, or reduced insulin secretion in response to an elevated blood glucose level. However, she observed that neither the whole pancreatic insulin content nor the glucose stimulated insulin secretion showed significant differences between the A0B2 and A0B0 mice. In contrast, the α-cell to β-cell ratio and double positive cells became remarkably higher in the A0B0 islets compared to the A0B2 islets, and she assumed that this abnormal α-cell/β-cell relationship could explain the relatively more impaired glucose tolerance in A0B0 mice than in A0B2 mice under normal diet conditions.

Based upon the above data, the author considered that on a C57BL/6J background under a normal diet, a deficiency of MafA alone was not sufficient to present the possible role of MafB in maintaining adult β-cell function. Therefore, she next implemented HFD treatment for mice, and observed drastic reduction in insulin positive cell numbers and severely impaired glucose tolerance together with symptoms of diabetes in A0B0 mice, while glucose stimulated insulin secretion showed no difference between A0B0 and A0B2 mice, indicating that critically damaged insulin production ability of β-cells can be thereason for A0B0 mice to become extremely glucose intolerant and develop diabetes. In addition to that, she observed total islet numbers were notably reduced and islet size failed to properly expand in the A0B0 pancreas.

（考察　**Discussion**）

Based on these observations, the author proposed that in insulin resistance disorders caused by obesity or gestation, the β-cell mass increases to adapt to the body’s increased requirements for insulin, which results in enlarged islets and increased islet numbers, and thatdeficiency of MafA in an HFD condition is harmful enough to cause insulin insensitivity in the body. The author speculated that removing MafB from β-cells will further inhibit the β-cell mass from expending itself by increasing the islet number and islet size.

（結論　**Conclusions**）

The author concluded that A0B0 mice become more susceptible to diabetes under HFD conditions with impaired

islet morphology and decreased insulin-expressing cell numbers, indicatingthat MafB plays as cryptic, but an important factor for adult pancreatic β-cell formation, unmasked under a MafA deficient condition in mice. She claims that this is the first study to show role of MafB in mature pancreatic β-cells in a certain pathological state using MafA and MafB double knock-out mouse in the β-cells, and that this finding can be appliedtohumans not only to understand type2 diabetes disease process, but also to provide MafB as a possible target for diabetic diseasetreatment.

審査の結果の要旨

Abstract of assessment result

（**批評　General Comments**）

This study is carefully designed based upon the previous report that MafB expression was induced in proliferative β-cell of the pregnant and HFD treated mice. Theauthor’s main observations are as follow. First, A0B0 adult mice displayed more severely impaired glucose tolerance compared to A0B2 mice. This phenomenon was further aggravated on HFD, which caused diabetes in the A0B0 mice. Second, deficiency of MafA has a destructive effect on normal islet structure, and moreover, this abnormality becomes more severe with the deletion of MafB. Third, a notable reduction in islets and islet cell numbers together with unsuccessful expansion of islet size was detected in HFD feeding A0B0 mice. The author’s findings suggest that MAFB could be a potential molecular targeted therapy to prevent diabetes through enhancing β-cell adaptive expansion during metabolic stress such as obesity and gestation.

（**最終試験の結果　Assessment**）

The final examination committee conducted a meeting as a final examination on July3, 2019. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（**結論　Conclusion**）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.